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TEAM LEADER EXAMINATION
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AUSTRALIA

Patents Act 1990

PROVISIONAL SPECIFICATION

Applicant(s):

THE UNIVERSITY OF SYDNEY

Invention Title:

COMPOSITION

The invention is described in the following statement:

COMPOSITION

FIELD OF THE INVENTION

The present invention relates to pharmaceutical compositions for the treatment of inflammatory conditions, and the use of such compositions for the treatment of inflammatory conditions in humans or animals. The compositions of the present invention contain a complex comprising a metal ion and a carboxylate ligand having anti-inflammatory action.

BACKGROUND

Non-steroidal anti-inflammatory drugs (NSAIDs) are used in the treatment of a variety of inflammatory conditions in humans and animals. NSAIDs are used to treat inflammatory conditions including rheumatoid arthritis, osteoarthritis, acute musculoskeletal disorders (such as tendonitis, sprains and strains), low back pain (commonly referred to as lumbago), and inflammation, pain and edema following surgical or non-surgical procedures.

However, many NSAIDs cause adverse effects in humans and animals, particularly adverse gastrointestinal effects. For example, indomethacin is a NSAID and is effective in treating inflammatory conditions in humans and animals. However, indomethacin can cause severe adverse gastrointestinal effects in humans and animals, particularly when administered orally. In humans, indomethacin can cause ulcerations in the oesophagus, stomach, duodenum and intestines, and some fatalities have been reported. In dogs, indomethacin causes fatal gastrointestinal haemorrhaging. These adverse effects have limited the use of many NSAIDs.

It has been found that for many NSAIDs, metal complexes of the NSAID cause less adverse side effects, and result in increased uptake of the drug, compared to the free NSAID.

For example, the oral administration of the Cu(II) complex of indomethacin bis(*N,N*-dimethylformamide)tetrakis-μ-(*O,O'*-Indo)dicopper(II) complex ($[Cu_2(Indo)_4(DMF)_2]$) has been found to cause less gastrointestinal toxicity than indomethacin; and it has been claimed that the complex has increased anti-inflammatory activity compared to indomethacin. The mechanism of the reduced

gastrointestinal toxicity has not been elucidated. However, it is believed that it is at least in part due to the complex being more lipophilic than indomethacin, which leads to greater absorption of the complex.

Compositions containing this complex sold under the name Cu-Algesic have been used in veterinary practice in Australia, New Zealand, South Africa and other countries. These compositions are in the form of a tablet or a paste.

The Cu-Algesic tablets comprise 2 mg of the complex and the excipients dextrose (24.8%), cellulose (35%), maize starch (25.6%), magnesium stearate (4.27%), Tixosil (a silica based flow enhancing agent) (4.27%) and purified starch (4.27%), where the percentages are percentages by weight of the composition. The Cu-Algesic paste composition comprises 200 mg/5 g of the complex dispersed in a gel (the gel consisting of carbopol™ (carboxylvinyl polymer) (1%), Nippasol M (*n*-propyl-4-hydroxybenzoate, a preservative) (0.5%), adjusted to pH ~ 7.0 by addition of NaOH solution (8.5% w/v) and water, where the percentages are percentages by weight of the composition). A similar paste formulation containing the complex $[Cu_2(Indo)_4(OH_2)_2]$ has also been used for the treatment of inflammatory conditions in animals. The Cu-Algesic tablets and the Cu-Algesic paste have been administered orally to dogs without causing fatal gastrointestinal haemorrhaging.

However, it has been found that while compositions containing metal complexes of NSAIDs generally cause less adverse gastrointestinal effects than compositions containing the free NSAID, such compositions often still cause some adverse gastrointestinal effects.

In addition, it has been found that some compositions containing metal complexes of NSAIDs, including the Cu-Algesic paste, are associated with variable amounts of adverse gastrointestinal effects depending on the batch of production and the storage time prior to use.

It would be desirable to provide a composition containing a metal complex of a NSAID that causes less adverse gastrointestinal effects than prior art compositions containing the free NSAID or prior art compositions containing the metal complex of the NSAID.

The complex [Cu_2(Indo)$_4$(DMF)$_2$] included in the Cu-Algesic tablets and Cu-Algesic paste contains the ligand *N,N*-dimethylformamide (DMF). This ligand is toxic to humans and animals, and irritates the eyes, skin and respiratory system, causes nausea, vomiting and colic, liver damage, hepatomegaly, hypertension and dermatitis. Due to the toxicity of DMF, the regulatory authorities responsible for approving veterinary and pharmaceutical compositions for sale in Australia and other countries do not, or are reluctant to, approve compositions containing DMF for veterinary or pharmaceutical use.

SUMMARY OF THE INVENTION

The present inventors have found that the adverse gastrointestinal effects observed with the prior art compositions containing metal complexes of NSAIDs are at least in part caused by free NSAID released from the complex during the preparation of the composition, the storage of the composition and/or when the composition is administered to a human or animal patient.

In a first aspect, the present invention provides a pharmaceutical composition comprising a metal complex of a carboxylate having anti-inflammatory activity in a pharmaceutically acceptable carrier, wherein

(1) the composition has a colloidal structure, or forms a colloidal structure when administered to a human or animal, or is immiscible with water;

(2) more than 80%, preferably more than 90%, and more preferably more than 95%, of the total amount of the carboxylate having anti-inflammatory activity in the composition is present as part of a metal complex; and

(3) less than 10% of the carboxylate having anti-inflammatory activity complexed with the metal dissociates from the metal over 12 months when the composition is stored in the absence of light at room temperature (18 to 25°C);

but excluding compositions comprising a complex containing the ligand DMF.

Preferably less than 10% of the carboxylate having anti-inflammatory activity complexed with the metal dissociates from the metal over 18 months, more preferably less than 5% over 18 months, and most preferably less than 5% over 2 years, when the composition is stored in the absence of light at room temperature.

In a second aspect, the present invention provides a method for treating an inflammatory condition in a human or animal, the method comprising administering to the human or animal a therapeutically effective amount of a composition according to the first aspect of the present invention. The animal may, for example, be a dog, a cat, a cow, a horse, etc. The composition may be administered orally, topically, by injection, by suppository, inhalation or by some other route.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1. Gastric mucosal ulcerogenic effects in rats after oral administration of solid-state IndoH (10 mg kg^{-1}), $[Cu_2(Indo)_4L_2]$ (L = DMF, Sample M; OH_2, Sample F, 11 mg kg^{-1}), MCT pastes of Sample F and Sample M $[Cu_2(Indo)_4L_2]$ (L = DMF, Sample M; OH_2, Sample F , 11 mg kg^{-1}), and a carbopol paste of Sample F $[Cu_2(Indo)_4(OH_2)_2]$ (11 mg kg^{-1}). Data are presented as the means ± sem (mm^2) between four rats per treatment group. A significant difference is found between the treatment group and control ($P < 0.05$(*), $P < 0.01$(**), and $P < 0.001$(***)).

Figure 2. Mucosal ulcerogenic effects in rats after oral administration of solid-state IndoH (10 mg kg^{-1}), $[Cu_2(Indo)_4L_2]$ (L = DMF, Sample M; OH_2, Sample F, 11 mg kg^{-1}), MCT pastes of Sample F and Sample M $[Cu_2(Indo)_4L_2]$ (L = DMF, Sample M; OH_2, Sample F , 11 mg kg^{-1}), in the small intestine. Data are presented as the means ± sem (mm^2) between four rats per treatment group. A significant difference is found between the control and treatment group ($P < 0.01$(**), $P < 0.001$(***)).

Figure 3. Anti-inflammatory effects after oral administration of a carbopol paste of Sample F ($[Cu_2(Indo)_4(OH_2)_2]$ (11 mg kg^{-1})) on edema formation induced in rat paws by carrageenan compared to controls. Data are presented as the means (±sem) of paw diameter change (Δmm) determined over 5 h between three rats per treatment group. A significant difference was found between the control and carbopol paste treatment animals ($P < 0.001$ (***)).

Figure 4. Anti-inflammatory effects after oral administration of an MCT paste of Sample F ($[Cu_2(Indo)_4(OH_2)_2]$ (11 mg kg^{-1})) on edema formation induced in rat paws by carrageenan compared to controls. Data are presented as the means (±sem) of paw diameter change (Δmm) determined over 5 h between three rats per treatment

group. A significant difference was found between the control and MCT paste treatment animals at $P < 0.05$ (*).

Figure 5. Anti-inflammatory effects after oral administration of IndoH (Sample I (10 mg kg^{-1})) in CMC (2%) solution on edema formation induced in rat paws by carrageenan compared to controls. Data are presented as the means (±sem) of paw diameter change (Δmm) determined over 5 h between three rats per treatment group. A significant difference was found between the control and MCT paste treatment animals at $P < 0.001$ (***).

Figure 6. Plot of the % inhibition after oral administration of solid-state Sample I (IndoH (10 mg kg^{-1})) and an MCT and carbopol paste of Sample F ($[Cu_2(Indo)_4(OH_2)_2]$ (11 mg kg^{-1})) on rat paw edema formation induced in rat paws by carrageenan. Data are presented as the means (± sem) of % inhibition in paw diameter determined over 5 h between three rats per treatment group relative to a control group. No differences were found in the % inhibition of edema between the treatment groups at $P > 0.05$.

DETAILED DESCRIPTION OF THE INVENTION

The metal complex of a carboxylate having anti-inflammatory activity ("the metal carboxylate complex") may be any complex comprising at least one metal ion and at least one carboxylate ligand having anti-inflammatory activity. The metal carboxylate complex may contain one or more carboxylate ligands having anti-inflammatory activity, and may contain one or more other ligands. The composition of the present invention may comprise a mixture of two or more different metal carboxylate complexes.

Typically the carboxylate having anti-inflammatory activity is a NSAID. Typically the metal is Cu, Zn, Co or Ni, preferably Cu.

Examples of copper complexes of NSAIDs include:

Copper-NSAID Complexes.

Compound	Structure
$[Cu_2(Asp)_4]$ [a]	Dimer

$[Cu(Asp)_2L_2]$,[a] where each L is independently selected and is benzimidazole, 2-methylbenzimidazole, metronidazole[b], 2-methylimidazole, 1,2-dimethylimidazole, pyridine, 3-picoline, 4-picoline, imidazole, 1-methylimidazole, diethylamine, nicotinamide, or *N*, *N*-dimethylsulfoxide	Monomer
$[Cu_2(Sup)_4(CH_3CN)_2]$ [c]	Dimer
$[Cu_2(Sup)_4(OH_2)_2]$ [c]	Dimer
$[Cu(Tol)_2(pyridine)_2]$ [d]	Monomer
$[Cu_2(Tol)_4(dmso)_2]$ [d,e]	Dimer
$[Cu(Nap)_2(pyridine)_2]$ [f]	Monomer
$[Cu_2(Nap)_4(dmso)_2]$ [e,f]	Dimer
$[Cu(Ibu)_2(pyridine)_2]$ [g]	Monomer
$[Cu_2(Ibu)_4(dmso)_4]$ [e,g]	Dimer
$[Cu(Ibu)_2(imidazole)_2]$ [g]	Monomer
$[Cu(Ibu)_2(2\text{-methylimidazole})_2]$ [g]	Monomer
$[Cu_2(Ibu)_4(caffeine)_2]$ [g]	Dimer
$[Cu_2(Ibu)_4(metronidazole)_2]$ [g]	Dimer
$[Cu_2(Flufen)_4L_2]$,[h] where each L is independently selected and is caffeine or papaverine.	Dimer
$[Cu(Flufen)_2L_2]$,[h] where each L is independently selected and is nicotine, nicotinamide or *N*,*N*-diethylnicotinamide.	Monomer
$[Cu(Nif)_2L_2]$,[i] where each L is independently selected and is 3-pyridylmethanol, or water.	Monomer, Polymer
$[Cu_2(Nif)_4(dmso)_2]$ [e,i]	Dimer
$[Cu_2(Indo)_4L_2]$,[j] where each L is independently selected and is water, *N*,*N*-dimethylacetamide, *N*-methyl-2-pyrrolidone, tetrahydrofuran, acetonitrile, acetone, or dimethylsulfoxide	Dimer

$[Cu_2(Dic)_4L_2]$,[k] where each L is independently selected and is water, ethanol, dimethylsulfoxide or methanol	Dimer

where

[a] Aspirin = 2-acetylsalicylic acid (AsaH);
[b] metronidazole = 2-methyl-5-nitrobenzimidazole;
[c] Suprofen = (+)-α-methyl-4-(2-thienyl-carbonyl)phenylacetic acid (SupH);
[d] Tolmentin = 1-methyl-5-(*p*-toluoyl)-1*H*-pyrrole-2-acetic acid (TolH);
[e] dmso = dimethylsulfoxide;
[f] Naproxen = 6-methoxy-α-methyl-2-naphthaleneacetic acid (NapH);
[g] Ibuprofen = (+)-α-methyl-4-(isopropylmethyl)benzeneacetic acid (IbuH);
[h] Flufenamic Acid = *N*-trifluoromethylphenyl)anthranilic acid) (FlufenH);
[i] Niflumic Acid = 2-(3-trifluoromethyl)phenylamino)-3-pyridine-carboxylic acid (NifH).
[j] Indomethacin = 1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indole-3-acetic acid (IndoH);
[k] Diclofenac = 2-[2, 6-dichlorophenyl)amino]phenyl acetic acid (DicH);

A new complex of Cu with a NSAID, $[Cu(tenox)_2(py)_2].EtOH$, is described in Moya-Hernandez MR, Mederos A, Dominguez S, et al., Speciation study of the anti-inflammatory drug tenoxicam (Htenox) with Cu(II): X-ray crystal structure of $[Cu(tenox)_2(py)_2].EtOH$, J. Inorg. Biochem. 95 (2-3): 131-140, June 1, 2003.

A preferred complex is $[Cu_2(Indo)_4(OH_2)_2].nH_2O$, when n is number of waters of crystallisation. The number of waters of crystallisation will vary depending on the technique used to prepare the complex, and is typically from 1 to 5.

The metal carboxylate complex may be prepared by methods known in the art. For example, Cu(II) complexes with indomethacin may be prepared as described in US patent no. 5,466,824 or as described in Anti-inflammatory Dinuclear Copper(II) Complexes with Indomethacin. Synthesis, Magnetism and EPR Spectroscopy; Crystal Structure of the *N,N*-Dimethylformamide Adduct. Weder, J. E.; Hambley, T. W.; Kennedy, B. J.; Lay, P. A.; MacLachlan, D.; Bramley, R.; Delfs, C. D.; Murray, K. S.; Moubaraki, B.; Warwick, B.; Biffin, J. R.; Regtop, H. L. *Inorg. Chem.* **1999**, *38*, 1736-1744.

In some embodiments, the composition has a colloidal structure. In some other embodiments, the composition is formulated such that when the composition is administered to a human or animal body by the intended route of administration, a composition having a colloidal structure is formed. Such a composition typically

forms a composition having a colloidal structure when the composition contacts an aqueous biological fluid in the human or animal body, for example, on contact with an aqueous fluid in the digestive tract.

A composition has a colloidal structure if it comprises a colloidal system. A colloidal system is a system in which particles of colloidal size of any nature (e.g. solid or liquid or gas) are dispersed in a continuous phase of a different composition (or state).

Various colloidal systems are known and some of these are summarised below:

Form of the colloidal particle	Form of the continuous phase	Type of colloidal system
Liquid	Gas	Liquid aerosol
Gas	Liquid	Foam
Liquid	Liquid	Emulsion
Solid	Liquid	Sol/suspension/hydrosol in water
Micelles	Liquid	Micelle solution
Liquid	Solid	Solid emulsion

The composition of the present invention may comprise any of the colloidal systems referred to above. In preferred embodiments, the composition comprises micelles in an aqueous carrier or is an oil-in-water emulsion, or forms micelles or an oil-in-water emulsion when the composition is administered to a human or animal body.

Without wishing to be bound by theory, it is believed that the colloidal structure protects the metal carboxylate complex from interaction with acids or other compounds which would otherwise interact with the complex to cause the complex to dissociate, thus reducing the amount of the complex that dissociates to form free carboxylate. In some embodiments of the present invention, the composition has a colloidal structure. It is believed that during storage of such a composition, the colloidal structure reduces the extent to which some compounds present in the composition are able to interact with the complex to cause the complex to dissociate. Similarly, it is believed that when such a composition is administered to a patient, the

colloidal structure limits the extent to which some compounds that come into contact with the composition after it is administered, e.g. compounds present in stomach acid for compositions administered orally, are able to interact with the complex to cause the complex to dissociate before it is absorbed through the gastrointestinal tract. In some other embodiments of the present invention, the composition does not have a colloidal structure but is formulated such that when the composition is administered to a human or animal body by the intended route of administration, a colloidal structure is formed. It is believed that the colloidal structure formed when the composition is administered limits the extent to which some compounds that come into contact with the composition after administration, e.g. compounds present in stomach acid for a composition administered orally, are able to interact with the complex to cause the complex to dissociate.

In some embodiments, the composition is immiscible with water, and is thus immiscible with aqueous biological fluids. Without wishing to be bound by theory, it is believed that when such a composition is administered to a human or animal, the immiscibility of the composition with aqueous biological fluids limits the extent to which some compounds that come into contact with the composition after administration are able to interact with the complex to cause the complex to dissociate.

In some embodiments of the present invention, the composition comprises micelles in an aqueous carrier, or is in the form of an oil-in-water emulsion. When such a composition is administered to a human or animal, for example, orally, topically, by injection, to the eye, etc, the composition typically maintains the colloidal structure for some time after administration.

When the composition comprises micelles in an aqueous carrier, the composition typically comprises water and an amount of one or more surfactants effective to form micelles in the aqueous carrier. Any surfactants that are capable of forming micelles in the aqueous carrier, that are pharmaceutically acceptable when administered by the intended route of administration, and that do not interact with the metal carboxylate complex to cause more than 10% of the carboxylate having anti-inflammatory activity complexed with the metal to dissociate from the metal when the composition is stored in the absence of light for 12 months at room temperature, may be used.

When the composition is in the form of an oil-in-water emulsion, the composition comprises one or more oils, one or more surfactants and water. Typically, the metal carboxylate complex is dissolved in the oil phase of the oil-in-water emulsion. The

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oil, surfactant and water may be any combination of oil(s), surfactant(s) and water that are capable of forming an oil-in-water emulsion, that are pharmaceutically acceptable when administered by the intended route of administration, and that do not interact with the complex to cause more than 10% of the carboxylate having anti-inflammatory activity complexed with the metal to dissociate from the metal when the composition is stored in the absence of light for 12 months at room temperature.

Suitable oils for compositions for oral or topical administration include, but are not limited to, triglycerides, particularly medium chain triglycerides, soy lethicin and paraffins. Such oils are suitable for use in compositions for oral or topical administration.

Suitable surfactants for compositions for oral or topical administration include, but are not limited to, the Sorbitan Fatty Acid Ester group of surfactants. Such surfactants comprise mono-, tri-, or partial esters of fatty acids such as oleic, lauric, palmic and stearic acids. Such surfactants include:

sorbitan trioleate	(Span 85),
sorbitan monooleate	(Span 80),
sorbitan tristearate	(Span 65),
sorbitan monostearate	(Span 60),
sorbitan monopalmitate	(Span 40), and
sorbitan monolaurate	(Span 20).

Other suitable surfactants include the macrogol (polyoxyethylene) esters and ethers. These surfactants include, but are not limited to, the Caster Oil Polyoxyethylene group of surfactants, such as Termul 1284. This group of surfactants comprise caster oil ethoxylate.

Other suitable surfactants in this class include the Polyoxyethylene Sorbitan Fatty Acid Esters group of surfactants, including:

polyoxyethylene (20) sorbitan monolaurate (Tween 20),
polyoxyethylene (4) sorbitan monolaurate (Tween 21), and
polyoxyethylene (20) sorbitan monooleate (Tween 80).

In a preferred embodiment of the present invention, the composition is a composition for oral administration comprising a metal complex of a NSAID, one or more pharmaceutically acceptable oils and one or more pharmaceutically acceptable surfactants, wherein

(1) the one or more oils and one or more surfactants are present in the composition in amounts such that following oral administration of the composition to a human or animal, the composition forms an oil-in-water emulsion on contact with aqueous fluids in the digestive system of the human or animal;

(2) more than 80%, preferably more than 90%, and more preferably more than 95%, of the total amount of the carboxylate having anti-inflammatory activity in the composition is present as part of a metal complex; and

(3) less than 10% of the carboxylate having anti-inflammatory activity complexed with the metal dissociates from the metal over 12 months when the composition is stored in the absence of light at room temperature;

but excluding compositions comprising a complex containing the ligand DMF.

A composition according to the preferred embodiment described above may optionally further comprise one or more solvents for increasing the solubility of the metal carboxylate complex in the composition. The solvent may, for example, be tetraglycol (IUPAC name: 2-[2-[(tetrahydro-2-furanyl)methoxy]ethoxy]ethanol; other names: 2-[2-(tetrahydrofurfuryloxy)ethoxy]ethanol; tetrahydrofurfuryldiethyleneglycol ether) or other glycofurols (also known as tetrahydrofurfurylpolyethyleneglycol ethers). The composition may also further comprise a thickener such as Aerosil 200, clay or another inorganic filler. Such a composition may for example comprise the following ingredients in the following amounts:

Ingredient:	Amount (% by weight):
One or more metal complexes of a NSAID	3 to 7
One or more glycofurols (e.g. tetraglycol)	30 ± 10%
One or more surfactants	10 ± 10%
One or more thickener	5 ± 10%
Medium chain triglyceride	50 ± 10%

An example of such a composition is a composition consisting of:

$[Cu_2(Indo)_4(OH_2)_2]$ complex	5.5% by weight
Tetraglycol	30% by weight
Termul 1284	10% by weight
Aerosil 200	5% by weight
Medium chain triglyceride	to 100% by weight

The present inventors have found that the oral administration of this composition causes greatly reduced adverse gastrointestinal effects than the oral administration of the equivalent amount of the free NSAID or a powder of the Cu-Indo complex. This composition also causes less adverse gastrointestinal effects than the oral administration of an equivalent amount of the prior art Cu-Algesic tablet or Cu-Algesic paste.

In some embodiments of the present invention, the composition is immiscible with water. Such compositions comprise the metal carboxylate complex in a hydrophobic pharmaceutically acceptable carrier. The hydrophobic carrier may be any hydrophobic carrier that is pharmaceutically acceptable by the intended route of administration and that does not interact with the complex to cause more than 10% of the carboxylate having anti-inflammatory activity complexed with the metal to dissociate from the metal when the composition is stored in the absence of light for 12 months at room temperature. Suitable hydrophobic carriers for a composition for oral or topical administration include, but are not limited to, oils such as triglycerides, soy lethicin and paraffins.

It is a feature of the present invention that more than 80%, preferably more than 90%, and more preferably more than 95%, of the total amount of the carboxylate having anti-inflammatory activity present in the composition is present as part of a metal complex, and that less than 10% of the carboxylate having anti-inflammatory activity complexed with the metal dissociates from the metal when the composition is stored for 12 months in the absence of light at room temperature. Compositions of the present invention having these features can be prepared by selecting suitable pharmaceutically acceptable carriers. For the Cu(II) complexes, the amount of the carboxylate present in the composition in the form of a metal complex can be readily determined by a person skilled in the art using methods known in the art, such as EPR spectroscopy.

The carrier for the composition of the present invention is selected such that the composition does not contain any ingredients or combinations of ingredients that

would react with the metal carboxylate complex so as to cause more than 10% of the carboxylate having anti-inflammatory activity complexed with the metal to dissociate from the metal when the composition is stored for 12 months in the absence of light at room temperature.

Strong chelating ligands such as peptides, certain carboxylate donors, reductants such as vitamins C and E, thiolate groups such as glutathione or cysteine containing species, can cause metal carboxylate complexes to dissociate. Accordingly, compositions according to the present invention preferably do not comprise, or are substantially free of, peptides, carboxylate donors, reductants and thiolate groups. Preferably the composition is not strongly acidic or basic as strong acids and bases can cause metal carboxylate complexes to dissociate.

An ingredient included in some oral pharmaceutical compositions is carboxylvinyl polymer. Carboxylvinyl polymer (sold under the name carbopol™) is included in the prior art Cu-Algesic paste. Carboxylvinyl polymer is used in pharmaceutical compositions for a variety of purposes including as a thickener. The present inventors have found that during the preparation and storage of pharmaceutical compositions containing a metal complex of a carboxylate having anti-inflammatory activity and carboxylvinyl polymer, some of the anti-inflammatory carboxylate dissociates from the complex, and accordingly, compositions according to the present invention preferably do not comprise, or are substantially free of, carboxylvinyl polymer.

Similarly, vitamin E is included in many topical ophthalmological compositions and other topical compositions as it helps repair damaged tissue in the eye or skin. However, vitamin E is a reductant, and causes metal carboxylate complexes to dissociate, and thus compositions according to the present invention preferably do not comprise, or are substantially free of, vitamin E.

The composition of the present invention comprises a metal carboxylate complex together with a pharmaceutically acceptable carrier. As used herein, a "pharmaceutically acceptable carrier" is a pharmaceutically acceptable solvent, suspending agent or vehicle for delivering the metal carboxylate complex to a human or animal. The carrier may be liquid or solid and is selected with the planned manner of administration in mind. The carrier must be pharmaceutically "acceptable" in the sense of being not biologically or otherwise undesirable, i.e. the carrier may be administered to a human or animal along with the active ingredient without causing any or a substantial adverse reaction.

Compositions of the present invention include those suitable for oral, rectal, nasal, topical (including buccal and sublingual), ophthalmological, vaginal or parenteral (including subcutaneous, intramuscular, intravenous and intradermal) administration. The composition may conveniently be presented in unit dosage form and may be prepared by methods well known in the art of pharmacy. Such methods include the step of bringing into association the metal carboxylate complex with the carrier. Typically the carrier consists of two or more ingredients. In general, the composition of the present invention is prepared by uniformly and intimately bringing into association the active ingredient with the carrier, and then if necessary shaping the product. Typically, the metal carboxylate complex and the one or more ingredients making up the carrier may be mixed in any order. However, it is preferred that the ingredients are mixed in a manner that minimises the amount of the metal carboxylate complex that dissociates during the preparation of the composition. When the composition is prepared by adding the metal carboxylate complex to a carrier comprising micelles in an aqueous system, the mixture of the metal carboxylate complex and the carrier may be sonicated on addition of the complex to the carrier to minimise dissociation of the complex before it goes into the micelles.

A composition of the present invention for oral administration may be in the form of a viscous paste, a tablet, a capsule, a chewable composition, or any other form suitable for oral administration. If desired, the composition may be encapsulated in a soft or hard capsule by techniques known in the art.

A composition for oral use may comprise one or more agents selected from the group of sweetening agents, disintegrants, lubricants, flavouring agents, colouring agents and preserving agents in order to produce pharmaceutically elegant and palatable preparations.

A chewable composition may for example comprise the metal carboxylate complex, one or more flavours, a base formulation, one or more preservatives, one or more pH modifiers, one or more desiccants and one or more fillers. For a chewable composition for horses, the base may comprise pre-gel starch, gelatine, flour and water. For example a chewable composition for horses may comprise the metal carboxylate complex, flavour, the base (comprising pre-gel starch, gelatine, flour and water), and other components including phosphoric acid, salt, sugar, sorbitol and/or glycerol, sorbic acid and/or potassium sorbate, benzoic acid, propionic acid and

maltodextrin. A chewable composition for dogs may comprise the metal carboxylate complex, meat emulsion, an acidulant (e.g. phosphoric acid), one or more antifungal agents (e.g. benzoic acid and sorbic acid), sugar or sugar alcohol, and salt.

A composition of the present invention for topical application may comprise the metal carboxylate complex in a conventional oil-in-water emulsion, water-in-oil emulsion, or water-immiscible pharmaceutical carrier suitable for topical application. Such carriers include for example, lacrilube, cetomacrogol cream BP, wool fat ointment BP or emulsifying ointment BP. Such carriers are in the form of an emulsion or are immiscible with water.

An example of a composition for topical application is a composition comprising 2% w/w $[Cu_2(Indo)_4(OH_2)_2]$ in an emulsifying cream, the emulsifying cream consisting of:

cetomacrogol emulsifying wax	15 g
liquid paraffin	10 g
white soft paraffin	10 g
chlorocresol	0.1 g
propylene glycol	5 ml
purified and cooled water	to 100 g.

Chlorocresol (4-chloro-3-methylphenol) is a preservative.

This composition is an oil-in-water emulsion.

Another example of a topical composition is a composition consisting of 2% w/w $[Cu_2(Indo)_4(OH_2)_2]$ in wool fat. This composition is immiscible with water.

Compositions for parenteral administration include compositions in the form of sterile aqueous or non-aqueous suspensions and emulsions.

In the compositions of the present invention containing a metal complex of a NSAID, more than 90%, preferably more than 95%, of the total amount of the NSAID in the composition is present in the composition in the form of a metal complex.

The composition of the present invention may include one or more pharmaceutically active ingredients in addition to the metal carboxylate complex.

Typically, the metal carboxylate complex constitutes about 0.1 to about 20% by weight of the composition.

The present invention also provides a method for treating an inflammatory condition in a human or animal, the method comprising administering to the human or animal a therapeutically effective amount of a composition according to the first aspect of the present invention. The composition may be administered orally, topically, by injection, by suppository, inhalation or by some other route.

The human or animal may be any human or animal having a disease or condition that requires treatment with a composition of the present invention. The animal is typically a mammal, and may be a non-human primate or non-primate. The mammal may for example be a companion animal such as a dog or cat, or a domestic animal such as a horse, pony, donkey, mule, llama, alpaca, pig, cow or sheep, or a zoo animal.

Suitable mammals include members of the Orders *Primates, Rodentia, Lagomorpha, Cetacea, Carnivora, Perissodactyla* and *Artiodactyla*.

For example, *Artiodactyla* comprises approximately 150 living species distributed through nine families: pigs (*Suidae*), peccaries (*Tayassuidae*), hippopotamuses (*Hippopotamidae*), camels (*Camelidae*), chevrotains (*Tragulidae*), giraffes and okapi (*Giraffidae*), deer (*Cervidae*), pronghorn (*Antilocapridae*), and cattle, sheep, goats and antelope (*Bovidae*). Many of these animals are used as feed animals in various countries. More importantly, many of the economically important animals such as goats, sheep, cattle and pigs have very similar biology and share high degrees of genomic homology.

The Order *Perissodactyla* comprises horses and donkeys, which are both economically important and closely related.

As used herein, the term "therapeutically effective amount" means an amount effective to yield a desired therapeutic response, for example, to prevent or treat an inflammatory condition. The specific "therapeutically effective amount" will vary with such factors as the particular condition being treated, the physical condition of the human or animal, the type of animal being treated, the duration of the treatment, the nature of concurrent therapy (if any), and the specific compositions employed and

the structure of the compound or its derivatives. The dosage administered and route of administration will be at the discretion of the attending clinician or veterinarian.

The invention is described below by reference to the following non-limiting examples. It will be appreciated by persons skilled in the art that numerous variations and/or modifications may be made to the invention as shown in the following Examples without departing from the spirit or scope of the invention as broadly described. The Examples are, therefore, to be considered in all respects as illustrative and not restrictive.

EXAMPLES

Example 1 - Preparation of [$Cu_2(Indo)_4(OH_2)_2$] complex

Cu(II) acetate monohydrate (0.028 g, 0.140 mmol) in water (0.75 ml) was added drop wise to indomethacin (0.1 g, 0.28 mmol) dissolved in ethanol (1.75 ml) at room temperature. Warming the ethanol mildly (~40 °C) helped solubilise the indomethacin before adding the copper acetate solution. On addition of the Cu(II) acetate monohydrate in water, bright green Cu-Indo/aqua complex fell out of solution immediately. This precipitate was filtered, washed with water and dried. Spectroscopic analysis shows that it was the [$Cu_2(Indo)_4(OH_2)_2$] complex, and EPR spectroscopy showed that it was >99% dimer.

The crystal size and colour of the Cu-aqua complex was checked with a light microscope. The crystals were found to be green in colour, with a star-like shape and 50-100 microns in diameter. This size was larger (by at least an order of magnitude) than the crystals prepared by the synthetic methods reported elsewhere.

Example 2 – composition

A composition of the present invention suitable for oral administration to animals or humans was prepared as described below.

The composition comprised the following ingredients:

Ingredient:	Amount:
[$Cu_2(Indo)_4(OH_2)_2$] complex	55.0 mg
Tetraglycol	300.0 mg

Termul 1284	100.0 mg
Aerosil 200	50.0 mg
Delios V MCT oil	qs 1.0 g

Delios V MCT oil is a medium chain triglyceride oil. Aerosil 200 is a silica based flow enhancing agent.

The composition was prepared as follows:

1. Add tetraglycol to mixer and heat to 75°C while stirring.
2. Add and dissolve Copper Indomethacin complex. Stir until dissolved, then remove heat.
3. Add Delios V MCT oil, while stirring.
4. Add Termul 1284, while stirring.
5. Add Aerosil 200 slowly, taking care to add it to the mixing vortex while bulk is still hot. Stir for 15 minutes until homogenous, then allow to cool.

The composition was a single phase paste and had the appearance and texture of a dark green paste.

When this formulation is administered orally to a human or animal, the composition forms an oil-in-water emulsion in the digestive tract.

This composition can be administered orally to treat inflammation in animals or humans.

<u>Example 3</u>

ELECTRON PARAMAGNETIC RESONANCE (EPR) SPECTROSCOPIC CHARACTERIZATION OF $[Cu_2(Indo)_4(OH_2)_2]$ IN PHARMACEUTICAL FORMULATIONS

The dissociation of the $[Cu_2(Indo)_4(OH_2)_2]$ complex results in the formation of the Cu(II) monomer and also a concomitant release of indomethacin. The relative amount of Cu(II) monomer compared to the amount of the complex $[Cu_2(Indo)_4(OH_2)_2]$ can, therefore, provide an indication of the amount of dissociation of the $[Cu_2(Indo)_4(OH_2)_2]$ complex in a pharmaceutical composition containing the $[Cu_2(Indo)_4(OH_2)_2]$ complex.

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The relative amount of the Cu(II) monomer in samples of various compositions containing the complex $[Cu_2(Indo)_4(OH_2)_2]$ was determined as described below. The compositions were the prior art *Cu-Algesic* tablets, the "*Cu-Algesic* granules" (the granules used in the preparation of the Cu-Algesic tablets), a formulation comprising the $[Cu_2(Indo)_4(OH_2)_2]$ complex in a carbopol gel (containing carbopol), and three compositions of the present invention, namely, the "*Cu-Algesic* MCT paste" (i.e. the composition of Example 2), the "*Cu-Algesic* eye ointment" (1% w/w $[Cu_2(Indo)_4(OH_2)_2]$ in lacrilube (white soft paraffin 57.3%, mineral oil (liquid paraffin) 42.5%, lanolin alcohols 0.2%) containing 1,1,1-trichloro-2-methyl-2-propanol (0.5%) as a preservative) and the "*Cu-Algesic* eye drops" (1% w/v $[Cu_2(Indo)_4(OH_2)_2]$ in an aqueous micelle of polyvinyl alcohol (14 mg/ml) and providone (6 mg/ml)). Each of these compositions was prepared by mixing the complex $[Cu_2(Indo)_4(OH_2)_2]$ with the appropriate carrier, and for each of the compositions there was no other possible source of the Cu(II) monomer other than the dissociation of the $[Cu_2(Indo)_4(OH_2)_2]$ complex. For the *Cu-Algesic* eye drops, the complex was sonicated with the aqueous micelle to ensure rapid dissolution into the micelle.

EPR Spectroscopy. Low temperature (4-110 K) X-band EPR spectra of the compositions containing $[Cu_2(Indo)_4(OH_2)_2]$ were measured at X-band frequencies (~9.5 GHz) using a Bruker EMX EPR spectrometer equipped with a standard ER4120 X band cavity, EMX 035M NMR gaussmeter, EMX 032T field controller, EMX 081 magnet power supply, Bruker EMX 048T microwave bridge control and BVT2000 variable temperature unit and Oxford Instruments E900 continuous flow cryostat (for low temperature data collection). Low temperature X-band EPR Cu(II) spectra of samples of $[Cu_2(Indo)_4(OH_2)_2]$ containing less than 0.47 mM Cu(II) were measured using a Bruker ESP 300 spectrometer equipped with a Hewlett Packard 5352B microwave frequency counter, Bruker ER 085C magnet power supply, Bruker ER 032 magnet field control, Bruker ER 023M signal channel and Bruker ESP 1600-1048 microwave bridge controller.

All Cu(II) monomer spectra used to quantify the percent of Cu(II) monomer content relative to the total initial Cu(II) content of the samples were collected at 4 K. Either a 100-µL solution or ~20 mg paste samples were placed in quartz EPR tubes (2-mm o.d., 1.5 mm i.d.) for data collection. Paste samples were placed into polyethylene tubes prior to insertion into the EPR tube. The Cu(II) monomer content relative to the total initial Cu(II) content of samples was calculated using the WINEPR data analysis

program (960801; Bruker: Franzen Analytik GmbH, 1990-1996) by determining the double integral (DI) of the Cu(II) monomer spectra of the solution/paste sample and comparing this to a $CuCl_2$ calibration curve. Samples for the $CuCl_2$ calibration were prepared in Milli-Q water using grade B volumetric glassware. Glycerin (20% w/w) was added to the $CuCl_2$ calibration samples to produce vitrified samples suitable for EPR spectroscopy. A spectrum of the empty resonator cavity and polyethylene paste sample holder were recorded prior to any Cu(II) calibration experiment to confirm a negligible contribution of the cavity and polyethylene sample holder to the sample spectra. The absence of signal saturation for the Cu(II) monomer spectra was checked by verifying a decrease in signal intensity by the square root of the microwave power with decreasing microwave power (Weber, R. T. *EMX User's Manual*; Bruker Instruments, Inc.: Billerica, 1995).

Results

The distinctive resonances for Cu(II) dimers due to the spin-triplet state are characterised by the spin Hamiltonian parameters $H_\perp$ (500 G), H_{z1}, (~4720 G) and H_{z2} (~5980 G). A small resonance at 3300 G due to a Cu(II) monomer fraction is also observed along with the seven-line (poorly defined) Cu-hyperfine coupling transitions on each of the $g_{||}$ signals (H_{z1}, and H_{z2}) (Weder, J. E.; Hambley, T. W.; Kennedy, B. J.; Lay, P. A.; MacLachlan, D.; Bramley, R.; Delfs, C. D.; Murray, K. S.; Moubaraki, B.; Warwick, B.; Biffin, J. R.; Regtop, H. L. *Inorg. Chem.* **1999**, *38*, 1736-1744). On cooling to 4 K, the Cu(II) monomer resonance increases and the Cu(II) dimer resonances ($H_\perp$, H_{z1}, and H_{z2}) disappears due to increased population of the diamagnetic ground state of the dimer, which has no EPR signal. X-band EPR spectroscopy of the samples in the 100-7000 G region were undertaken, therefore, to check for the presence of the dimer drug and any paramagnetic impurities.

The amount of the Cu(II) monomer in the samples, expressed as a percentage of the total amount of Cu in the composition is shown in Table 1. No quantitative results could be obtained for the *Cu-Algesic* tablets, or the *Cu-Algesic* granules in the solid state, but comparison of the EPR spectra with solutions and paste samples under the same conditions indicated that the Cu(II) content in these compositions was almost all in the form of the dimer.

The three compositions of the present invention (the *Cu-Algesic* MCT paste, eye ointment and eye drops) all contained less than 10% Cu(II) monomer fraction (Table 1). The carbopol gel formulation provided from the factory, however, contains

a significant fraction of Cu(II) monomer (80% of total Cu) due to the breakdown of the dimer structure. Other freshly prepared samples had lower amounts of the Cu(II) monomer (20-30% of total Cu).

Table 1. X-band EPR spectroscopic results of the veterinary formulations of $[Cu_2(Indo)_4L_2]$ ($L = OH_2$).

Formulation	Cu(II) monomer (%)
Cu-Algesic tablets	–[a]
Cu-Algesic granules	–[a]
Cu-Algesic MCT paste	6
Cu-Algesic eye ointment	< 1
Cu-Algesic eye drops	1
carbopol gel	80

[a] The technique is not applicable to dry powders, however, solid-state $[Cu_2(Indo)_4L_2]$ ($L = OH_2$) contains < 1% Cu(II) monomer fraction.

Cu-Algesic MCT paste: micellular medium chain triglyceride (MCT) paste
Cu-Algesic eye ointment: pharmaceutical-grade eye ointment base consisting of paraffins; including chorbutol (1,1,1-trichloro-2-methyl-2-propanol (0.5%)) as a preservative.
Cu-Algesic eye drops: aqueous micelle solution

Example 4

EFFICACY AND SAFETY IN RATS: A COMPARISON OF DIFFERENT PHARMACEUTICAL FORMULATIONS

This example compared the efficacy and safety of the Samples and compositions described below in a series of *in vivo* studies for the assessment of the Samples and compositions as anti-inflammatory agents and for their ability to induce acute gastrointestinal ulceration.

Test Samples:

Sample I = IndoH
Sample F = $[Cu_2(Indo)_4(OH_2)_2]$
Sample M = $[Cu_2(Indo)_4(DMF)_2]$ in a micronized form

The above Samples are described below as being solid-state, meaning the free compound not contained within a carrier or excipient mix. A composition containing Sample F in a carbopol paste was prepared by mixing Sample F with a carbopol paste carrier (the carrier consisting of carbopol, a preservative, water and a sufficient amount of a NaOH solution to adjust the pH to ~ 7.0). A composition containing Sample F in a MCT paste was prepared as described in Example 2. A composition containing Sample M in a MCT paste was prepared in the same manner using Sample M instead of Sample F. Reference is also made below to a micronized Sample, which means the Sample is manufactured using the technique know as super critical fluid GAS methods that results in fine particulates of the compound (Warwick, B.; Dehghani, F.; Foster, N. R.; Biffin, J. R.; Regtop, H. L. Micronization of Copper Indomethacin Using Gas Antisolvent Processes. *Ind. Eng. Chem. Res.* **2002**, *41*, 1993-2004).

The Samples and compositions were tested for their ability to inhibit in an inflammatory model, the carrageenan-induced paw edema model, and were also tested in a gastrointestinal ulceration model as described below.

Methods:

Samples. The carbopol pastes were freshly prepared and typically exhibited only 20-30% decomposition of the dimer to Cu(II) as shown by EPR spectroscopy.

Animals. Sprague-Dawley rats weighing 200-250 g were used throughout these studies (supplied by the laboratory animal services at the University of Sydney). Animals were housed in polypropylene cages and allowed free access to standard laboratory rat chow (Purina Rat Chow, Ralston Purina, St Louis MO, USA) and tap water. Animals were housed in the animal care facility of the Faculty of Pharmacy at ambient temperature and humidity with a 12-h light-dark cycle. The experimental animal protocols were approved by the Animal Ethics Committee of the University of Sydney in July 1999, approval number L24/7-99/3/2972.

Gastrointestinal Ulceration: To assess gastric damage, rats ($n = 4$ per group) were fasted overnight with free access to water prior to the oral administration (non-anaesthetized) of the formulations via oral gavage. Three hours after administration of the above-mentioned doses, the rats were euthanased and the stomach was excised and opened by incision along the greater curvature. The stomach was rinsed,

submerged in 10% formaldehyde for 1 h and examined to determine the extent of macroscopic gastric damage. The damage is reported as the summation of the area of macroscopic ulcerations (mm^2).

Rats ($n = 4$) were allowed free access to food and water prior to and during the assessment of damage to the small intestine. At 24 h after dosing, the entire small intestine was excised and flushed with water to expel the intestinal contents. The entire small intestine was examined from 10 cm distal to the ligament of Treitz to the ileocecal junction and the damage is reported as the summation of the area of macroscopic ulcerations (mm^2). The total volume of the MCT or carbopol paste administered per dose in the assessment of gastrointestinal ulceration was no more than 0.5 g.

Inhibition of Carrageenan-Induced Paw Edema: The control cohort was dosed solely with CMC (2%) solution. Inflammation was induced one hour after dosing with the NSAID (or vehicle), by injecting with carrageenan (0.1 mL, 2% w/v in isotonic saline) into the plantar region of the hind paw ($n = 3$) (Winter, C. A.; Flataker, L., *Pharmacol. Exp. Ther.* **1965**, *150*, 165-171). The thickness of the paw was measured at the ventral dorsal footpad using digital calipers prior to dosing and at 3 and 5 h after carrageenan injection. The change in the measured parameter (ΔP) for thickness of paw (Δmm) at n = 3- and 5-hours after carrageenan injection is given by:

$$\Delta P = P_{t=n} - P_{t=0} \qquad \text{(I)}$$

The percent inhibition (% inhibition) at 3- or 5-hours in the measured parameter (P) due to the treatment is given as the difference between the % increase in the value of P in the control group and the treatment group at n = 3- or 5-hours, with the % increase in the value of P given by:

$$[(P_{t=n} - P_{n=0}) \div P_{n=0}] \cdot 100 \qquad \text{(II)}$$

Statistical analysis: All inhibition of carrageenan-induced paw edema and gastrointestinal ulceration data are expressed as the standard error of the mean (±sem). Comparisons among the control and treatment groups were made using one-way analysis of variance followed by a Student-Newman-Keuls *t*-test using the GraphPad Instat statistical program. With all analyses, an associated probability (P-value) of less than 5% (P-value < 0.05) was considered significant. The calculation of the power of the experiment to compare two treatment groups with a P-value threshold of 0.05 was determined using the GraphPad StatMate program (*GraphPad Instat*; version 3.01 for WIN95/NT, GraphPad Software Inc., 1998).

Results

Acute GI Ulceration: Data of mean (±sem) acute gastric and small intestine ulceration (mm^2) due to the various formulations are given in Table 2. Oral administration of solid-state IndoH (10 mg kg^{-1}) provoked significant hemorrhagic lesions in the stomach (28.0±1.7 mm^2, P < 0.01) and small intestine (177.0±4.4 mm^2, $P < 0.001$) compared to the control cohort (0.25±0.25 mm^2 in the stomach, and 0.5±0.5 mm^2 in the small intestine). While no significant ulceration (P > 0.05) was found between the control and solid state Sample F treated animal in the assessment of acute gastric damage (mm^2), significant ulceration was found in the assessment of acute intestinal ulceration between the control and solid-state Sample F treatment (61.0±34.5 mm^2, P < 0.01). There was, however, a significant reduction in intestinal ulceration observed following the administration of solid-state $[Cu_2(Indo)_4(OH_2)_2]$ (Sample F) compared to solid-state IndoH (Sample I) at P < 0.001. Gastric and small intestinal mucosal ulcerogenic effects of the formulations are shown in Figures 1 and 2, respectively.

In contrast, solid-state micronized $[Cu_2(Indo)_4(DMF)_2]$ (Sample M) dosed at ~11 mg kg^{-1} (equipotent to IndoH dosed at 10 mg kg^{-1}) produced significant gastropathy in the stomach (P < 0.001, 49±7 mm^2) but not in the small intestine (P > 0.05, 8.7±2.9 mm^2) compared to the control animals. In addition, solid-state Sample M caused significantly more gastropathy (49.0±6.7 mm^2) than solid-state IndoH (28.0±1.7 mm^2, P < 0.01) or solid state Sample F (7.8±2.7 mm^2, P < 0.05). The administration of an MCT paste or carbopol paste of Sample F resulted in significantly less gastric ulceration compared to solid-state micronized $[Cu_2(Indo)_4(DMF_2)_2]$ (Sample M) (P < 0.001). The intestinal protective effects of Sample F and the MCT paste of Sample F is highlighted by extremely significant and conclusively less intestinal ulceration (mm^2) compared to solid-state IndoH at P-values < 0.001. In addition, the MCT paste of Sample F afforded a greater protection from intestinal ulceration than the solid-state form of Sample F, with a significant reduction in intestinal ulceration (mm^2) observed for the MCT paste of Sample F compared to the solid-state Sample F (P < 0.01). Solid-state IndoH was significantly more ulcerogenic in the small intestine compared to solid-state Sample F or Sample M (P < 0.001), and solid-state Sample M was significantly less ulcerogenic in the small intestine compared to solid-state Sample F (P < 0.001). The fact that the MCT paste formulation reduces small intestine ulceration by an order of magnitude (back to

control levels) compared to the same complex in carbopol paste is consistent with the release of ~20% of free Indo in the carbopol paste due to degradation of the dimer. This makes the MCT pastes far superior in terms of safety in sensitive species such as dogs, particularly when compared with some of the carbopol pastes that had up to 80% of the Cu(II) dimer broken down into Cu(II) monomer and free Indo. Although these highly degraded formulations were not tested, they would have had greatly increased GI toxicity as evident by the increase in GI toxicity when much smaller amounts of free Indo were released.

Inhibition of Carrageenan-Induced Paw Edema: The intraplantar injection of carrageenan (0.1 mL of 2% solution) elicited acute hind-paw inflammation and caused a time-dependent increase in paw edema as measured by rat paw diameter change (Δmm). A peak inflammatory response was observed at 3 h after the injection (Figures 3, 4 and 5). No significant difference ($P > 0.05$) was observed in paw edema change (Δmm) between the control groups at 3- and 5-hours post-carrageenan injection.

Treatment of animals with IndoH (10 mg kg^{-1}) in CMC (2%) solution suppressed the paw diameter change (Δmm); with the % inhibition in paw diameter change relative to the control cohort being 21(8)% and 25(6)% at 3- and 5-hours, respectively (Table 3 and Figure 6). Likewise, the carbopol and MCT pastes of $[Cu_2(Indo)_4(OH_2)_2]$ (11 mg kg^{-1}) prepared from Sample F resulted in percent inhibition in paw diameter change relative to the control cohort at 3- and 5-hours of 28(3)% (3-hr) and 27(4)% (5-hr) for the former and 22(10)% (3-hr) and 28(8)% (5-hr) for the latter (Table 2 and Figure 6). The greater the value of the % inhibition in rat paw diameter change, the greater is the anti-inflammatory effect of the treatment. There was a significant difference in paw diameter change (Δmm) as a result of treatment with MCT ($P < 0.05$) or carbopol ($P < 0.001$) pastes of Sample F compared to control at 3- and 5-hours post-carrageenan injection (Figures 10 and 11). This result indicates both Cu-Indo pastes elicited anti-inflammatory effects, despite their different Cu(II) dimer contents.

A significant difference was found between the control cohort and the IndoH (10 mg kg^{-1}) in CMC (2%) solution treated group. No significant difference was found, however, between the anti-inflammatory efficacy of the MCT and carbopol paste treatments and IndoH in CMC (2%) solution treatment as assessed by changes in rat paw diameter (% inhibition) at 3 and 5- hours post-carrageenan injection

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($P < 0.05$). A plot of the anti-inflammatory efficacy of the treatments (as represented by % inhibition of edema) is shown in Figure 6.

Discussion and Conclusion

The present study showed that supratherapeutic doses of a non-micronized $[Cu_2(Indo)_4(OH_2)_2]$ was significantly less toxic in both the stomach and intestine than equimolar doses of the parent NSAID (IndoH); with the Cu(II) complex affording a significant anti-inflammatory effect similar to IndoH. Furthermore, the nature of the pharmaceutical formulation influenced the extent of the complexes GI-protective effect, with the incorporation of the Cu(II) complex of Indo into a GI protective paste further augmenting a significant reduction in GI toxicity compared to IndoH. It is known that formulation is important when considering not only the efficacy and toxicity of the drug, but also its pharmacokinetics.

Whilst particle shape can influence surface area, the most probable cause of the enhanced GI toxicity in the stomach of the rats following administration of the solid-state micronised dose of $[Cu_2(Indo)_4(DMF)_2]$ (Sample M) compared to solid-state factory grade $[Cu_2(Indo)_4(OH_2)_2]$ (Sample F) is increased degradation of Sample M to free IndoH due to an increased surface area of the administered dose. The increase in the surface area of the administered dose of Sample M is a result of the smaller mean surface area of the micronized particles manufactured by the super critical fluid GAS system compared to the factory grade aggregates (Sample F) produced from the conventional factory grade process. There was a significant difference in the values of both the surface area (μm^2) and circularity parameter ($P < 0.001$) of the particle sizes of Sample M compared to Sample F.

The acute stomach toxicity of solid-state micronized $[Cu_2(Indo)_4(DMF)_2]$ was significantly reduced by the formulation of the particles into an MCT paste, probably due to a protective gastric barrier afforded by the paste and the stability of the complex within the formulation.

Whilst the Cu(II) dimer complex of Indo is retained in the MCT paste compared to the carbopol paste, no significant difference was found between the anti-inflammatory efficacy of the MCT or carbopol paste treatments as assessed by changes in rat paw diameter (Δmm) in both treatment groups at 3 and 5- hours post-carrageenan-induced paw edema ($P > 0.05$). This may be due to the lack of sufficient sensitivity of the anti-inflammatory assay to differentiate between the efficacies of the treatments,

achievement of equivalent plasma and tissue concentrations between the formulations or the administration of a supratherapeutic dose being near the effective maximum anti-inflammatory dose. Nonetheless, both the MCT (2% Cu(II) monomer content) and carbopol (20% Cu(II) monomer content) pastes of Sample F afforded equipotent anti-inflammatory activity compared to the control group.

The acute direct toxicity of NSAIDs in the small intestine is highlighted by the highly significant intestinal ulceration observed following the administration of solid-state IndoH (Sample I) compared to the control cohort. The present study confirmed a highly significant ulcerogenic-sparing activity in the intestine of solid-state $[Cu_2(Indo)_4(OH_2)_2]$ compared to solid-state IndoH (P-value < 0.001). This result is contrary to an early report by others of unaltered ulcerative damage by IndoH when given as a Cu(II) complex (Boyle, E.; Freeman, P. C.; Goudie, A. C.; Mangan, F. R.; Thomson, M., *J. Pharm. Pharmac.* **1976**, *28*, 865-868). Furthermore, there was an additional increase in small intestine protection when the dimeric Cu(II) complex of Indo was formulated into an MCT paste rather than administered to the animals as a powdered dose form of the Cu(II) complex of Indo. Instability of $[Cu_2(Indo)_4(OH)_2]$ in the stomach is best avoided in order to prevent degradation of the ulcerogenic-sparing Cu complex of Indo to free IndoH (which has significant ulcerogenic side-effects in both the stomach and intestine). This was evidenced by the enhanced gastropathy caused by the micronized solid-state compared to factory grade solid-state Cu(II) complex, which was ameliorated by its formulation into an MCT paste.

The administration of the solid-state micronized Cu(II) complex of Indo caused significantly less toxicity in the small intestine than solid-state IndoH or solid-state $[Cu_2(Indo)_4(OH_2)_2]$, possibly due to the enhanced absorption of free IndoH from the stomach following the disintegration of the Cu(II) dimer complex. Enhanced bioavailability of drugs due to GI mucosal damage is reported elsewhere, e.g., following administration of "permeability enhancers" such as 5-methoxysalicylate (Peters, G. E.; Hutchinson, I. E. F.; Hyde, R.; McMartin, C.; Metcalfe, S. B. *J. Pharm. Sci.* **1987**, *76*, 857). The acute gastric toxicity of the micronized sample of $[Cu_2(Indo)_4(DMF)_2]$ compared to solid-state IndoH was no doubt due to the increased surface area of the micronized dose of $[Cu_2(Indo)_4(DMF)_2]$ (particle size $2.98 \pm 1.24\ \mu m^2$) compared to IndoH (particle size $226 \pm 19\ \mu m^2$).

The acute gastropathy associated with the administration of micronized $[Cu_2(Indo)_4(DMF)_2]$ further highlights the importance of characterizing the pharmaceutical nature of the veterinary formulation and ensuring the retention of the

Cu(II) complex in the GI tract. Whilst the current work confirmed the GI-sparing toxicity of the Cu(II) complex of Indo compared to the parent NSAID as reported by others (Sorenson, J. R. J., *Prog. Med. Chem.* **1989**, *26*, 437- 568), the carrageenan-induced rat paw edema results are unable to verify an enhanced anti-inflammatory potency of the Cu-Indo complex compared to IndoH.

In summary, the nature of the formulation does not appear to have a large effect on the efficacy of the Indo pharmaceuticals, but it has a dramatic effect on the GI toxicity. The micronized Cu-Indo is highly GI toxic, like IndoH since its large surface area allows for easy acid-induced breakdown to free IndoH in the stomach. The larger crystals present in more standard preparations induce considerably less ulceration, but the greatest GI protection is obtained with the composition of the present invention (Sample F in the MCT paste). While there is no difference in gastric protection between fresh carbopol pastes containing only 20% dissociation of Cu-Indo and MCT pastes, there is an order of magnitude decrease in small intestine toxicity in the MCT paste over the carbopol pastes, no doubt due to the increased levels of free indomethacin in the carbopol paste. Moreover, the Cu-Indo dimer degradation during formulation and soon afterwards in the carbopol pastes shows a large variation between batches, as observed by visual changes in the colour of the paste and by EPR spectroscopy determination of the dimer content. This leads to an increase in free Indo, which makes this less suitable as a pharmaceutical formulation, especially for the treatment of species that are sensitive to free IndoH, such as dogs. Even for the carbopol formulations with the least decomposition of dimer (20%), the carbopol paste is more GI toxic than the MCT paste. The carbopol batches with up to 80% decomposition of the Cu(II) dimer, with consequential release of free Indo, are expected to be almost as GI toxic as similar formulations with Indo only.

Table 2. Data of mean acute gastric and small intestine ulceration ±sem (mm^2).

Control ($n = 4$)	IndoH solid-state (Sample I) ($n = 4$)	$[Cu_2(Indo)_4(OH_2)_2]$ solid-state (Sample F) ($n = 4$)	$[Cu_2(Indo)_4(DMF)_2]$ solid-state (Sample M) ($n = 3$)	Carbopol paste of Sample F ($n = 4$)	MCT paste of Sample F ($n = 4$)	MCT paste of Sample M ($n = 4$)
Gastric ulceration (mm^2)						
0.25±0.25	28.0±1.7	7.8±2.7	49.0±6.7	6.8±1.7	6.3±2.4	23.3±10.9
Small intestine ulceration (mm^2)						
Control ($n = 4$)	IndoH solid-state (Sample I) ($n = 3$)	$[Cu_2(Indo)_4(OH_2)_2]$ solid-state (Sample F) ($n = 3$)	$[Cu_2(Indo)_4(DMF)_2]$ solid-state (Sample M) ($n = 3$)	Carbopol paste of Sample F ($n = 4$)	MCT paste of Sample F ($n = 4$)	MCT paste of Sample M ($n = 4$)
0.50±0.50	177.0±4.4	61.0±34.5	8.7±2.9	6.0±0.9	0.5±0.3	0.25±0.25

Table 3. The percent inhibition in rat hind-paw diameter change due to treatment 3- and 5-hours post intraplantar injection of carrageenan (0.1 mL of 2% solution).

Treatment	3-hr	5-hr
Indomethacin (10 mg kg^{-1}) in CMC (2%) solution	21(8)%	25(6)%
$[Cu_2(Indo)_4(OH_2)_2]$ (11 mg kg^{-1}) in CMC (2%) solution [a]	30(4)%	31(3)%
MCT paste of $[Cu_2(Indo)_4(OH_2)_2]$ (11 mg kg^{-1}) [a]	28(3)%	27(4)%
Carbopol paste of $[Cu_2(Indo)_4(OH_2)_2]$ (11 mg kg^{-1}) [a]	22(10)%	28(8)%

[a] Sample F (factory grade).

Example 5

CU-ALGESIC FORTE PASTE: BIOEQUIVALENCE STUDY

This example compared the bioavailabilty of indomethacin in a composition of the present invention (Test Substance B) with a previously developed composition containing the same metal complex of indomethacin (Test Substance A). Both Test Substance A and Test Substance B contained the complex $[Cu_2(Indo)_4(OH_2)_2]$. Test Substance B was the composition prepared as described in Example 2. Test Substance A was a composition comprising the complex in a carbopol paste. Test Substance A is a commercially available paste formulation used in Australia for the treatment of animals. Test Substance A, whilst efficacious, was variable in its efficacy and tolerability.

1.1 Sample Analysis and Statistical Analysis

Centre for Heavy Metals Research, School of Chemistry, University of Sydney.

1.2 Study Location/Test Facility

Rural Veterinary Centre, University of Sydney Large Animal Hospital, Werombi Rd., Werombi.

1.3 Study Schedule

Experimental start date:

27/11/01 (1^{st} treatment)

17/12/01 (2^{nd} treatment)

Experimental end date:

25/12/01 (final sampling time)
15/5/02 (final sample analysis)

2. Materials and Methods

2.1 Study Design

The study design was based on the FDA Guidance for Industry Bioequivalence Guidance.

2.1.1 Treatment Groups

Two groups of 4 horses.

2.1.2 Experimental Design/Blocking:

The two pastes, old and new formulations (A and B) were administered in the experiment using a randomised cross-over design as outlined in the following table:

Horse	Treatment period 1	Treatment period 2
1	A	B
2	A	B
3	A	B
4	A	B
5	B	A
6	B	A
7	B	A
8	B	A

2.1.3 Wash-out period

A wash-out period of 20 days was used, based on the FDA Guidance which recommends a wash-out period of 10x the plasma half-life to provide for 99.9% of the administered dose to be eliminated from the body.

2.1.4 Randomisation and Allocation Procedures

Horses were randomly assigned to each group.

2.1.5 Blinding

As the experiment involved only blood collection, only the analyst was blinded, serum sample tubes were labelled with horse number only.

2.2 Animal Selection and Identification

2.2.1 Details of animals

Eight standard-bred mares aged between 5 and 8 years were used in the experiment.

2.2.2 Preparation of animals

All horses were given anthelmintic treatment and tetanus prophylaxis 7 days prior to the trial.

2.3 Animal housing and management

2.3.1 Housing and management

Horses were placed in pairs in 4 dirt yards with secure pipe fencing. Horses were returned to the paddock for a washout period of 20 days. The horses were brought up into the yards the night before the second treatment period.

2.3.2 Feed

All horses had free access to food (hay) and water throughout the experimental period. Horses were fed on night prior to trial and were fed immediately after drug administration at each of the two drug administration days.

2.3.3 Animal Handling

Veterinarians or staff at RVC.

2.3.4 Removal of Subject(s) from the study

Horses who developed any illness or trauma requiring medication were to be removed from the study. No horses had to be removed from the study.

2.3.5 Concurrent Therapies

No other medication, particularly NSAIDs, was permitted.

2.3.6 Owner Consent

The horses were owned by the Rural Vet Centre.

2.4 Treatments

Test Substance A

Active Ingredient:	Copper Indomethacin
Formulation:	
Copper Indomethacin	40.0 g/kg
Carbopol	10.0 g/kg
Methyl Hydroxybenzoate	3.0 g/kg
Propyl Hydroxybenzoate	1.0 g/kg
Potable Water	Qs ad 1 kg

Test Substance B

Active Ingredient:	Copper Indomethacin
Formulation:	
Copper Indomethacin	55.0 g/kg
Tetra Glycol	300.0 g/kg
Termul 1284	100.0 g/kg
Aerosil	50.0 g/kg
Delios (MCT)	Qs ad 1 kg

2.4.3 Drug Administration

Dosing regimen: 0.8 mg/kg, calculate dose based on weight

Route of administration: Oral

Wash-out period: 20 days

2.5 Test samples

2.5.1 Blood sample collection

On the morning of the trial, a 14 gauge over the needle catheter and T port was placed aseptically into the left jugular vein and secured with quick set glue and suture. The catheters were flushed with heparinized saline.

A 20-ml blood sample (time 0) was collected immediately prior to administration of the paste and placed into 2 serum tubes. Further samples were taken at 1 hr intervals

for 18 hours and then at 2 hour intervals until 24 hours (0,1,2,3...18,20,22,24). Catheters were flushed after each collection period with heparinized saline. Catheters were removed after the 24 hr collection and further samples were taken aseptically by venipuncture at 48, 96 and 192 hours post administration of each test drug. A 20-ml aliquot (one blood tube full) was collected at each sampling time into serum tubes labeled with horse ID number/name, sampling time (0,1 hr etc.) and date. Sample collection time was recorded on a data sheet and each time point was initialled.

Horses were returned to the paddock for a washout period of 20 days. The horses were brought up into the yards the night before the second treatment period. Catheters were placed in the right jugular vein the morning of the trial. Horses that received paste A in the first treatment period received paste B in the second treatment period and horses receiving paste B in the first treatment period received paste A as outlined in the table. Blood samples were collected at the same time intervals and the serum aseptically harvested and frozen for assay.

2.5.2 Sample handling

All serum samples were immediately spun down in a centrifuge at 3000 rpm for 10 minutes and the serum aseptically collected into labelled specimen tubes and frozen until assayed.

Samples were stored in a secure location in the freezer until transported to University of Sydney, School of Chemistry for analysis.

<u>2.6 Sample Analysis, HPLC</u>

2.6.1 Materials and reagents

Indomethacin for standards, Mefanamic acid and Acemethacin for internal standards were of pharmaceutical grade (Sigma Pharmaceuticals). Methanol and acetonitrile were of HPLC grade (Aldrich). Acetic acid was analytical grade (Aldrich). Purified water was obtained using a Milli-Q reagent water system (Millipore).

2.6.2 Gradient HPLC analysis

The analysis was performed on a Hewlett-Packard HPLC Series HP1100 with Diode-Array UV/VIS detector. Separation was achieved using a 5-μm RP- ZORBAX XDB-C_{18}, (250x4.6 mm I.D) column (Hewlett-Packard) equipped with a 5-μm ODS guard

column (Hewlett-Packard). The flow rate was 1 ml/min and the monitoring wavelength was 254 nm and 270 nm. A linear gradient, from 60% to 85% solvent B over 22 min was performed (solvent A: 0.5 % acetic acid in water; solvent B: 0.5 % acetic acid in a mixture of acetonitrile and methanol 1:1).

2.6.3 Sample Preparation

Horse plasma samples (1 ml) buffered to pH 3.5, were deproteinized with 5 ml acetonitrile, centrifuged at 3000 *g*. The supernatant were evaporated to dryness under nitrogen flow and reconstituted in mobile phase (100 μl) and aliquots of 20 μl were injected.

2.6.4 Calibration curves

The calibration curve for indomethacin in plasma was constructed by spiking blank horse plasma with known concentrations of 5, 10, 20, 50, 100, 200, 500, 1000, 1500 and 2000 ng/ml. A typical calibration curve of indomethacin was described by the equation $y = 6.88636e\text{-}1x + 2.09520e\text{-}1$ ($r = 0.99918$). In the equation, y represents the peak-area ration of the analyte to I.S., where x correspond to plasma concentration in ng/ml.

2.6.5 Quality control

Quality control was performed at level 10, 100, 1000 ng/ml during HPLC analysis of each horse plasma sample.

<u>2.7 Statistical Analysis</u>

The data were analysed to determine AUC values with WinNonlin version 1 software, using a non-compartment model. The area under plasma concentration *vs* time was estimated by linear/log trapezoidal approximation from 0 to 24 h, 0 to 48 h, 0 to 96 or 0 to 192 h.

In all horses the level of indomethacin had reached baseline levels after 24 hours and, therefore, all discussion hereafter is based on the analysis of the data up to the 24-hour time-point. Statistical analysis of the data was carried out using Student's *t* tests according to the FDA guidelines and using non-parametric tests which are more appropriate for a data set of this type. Analysis involved comparing the AUC for each of the two test substances (A & B), bioequivalence requires a non-significant difference between AUC for each formulation.

3. Results and Discussion

The data for all horses showed a pattern with multiple peaks in the indomethacin levels with the peak level occurring at 1-9 hours and the baseline level reached after 24 hours. Substantial inter-horse variation is observed, particularly in the AUC values suggesting variable uptake of the drug from the stomach. It is notable that the pattern of inter-horse variation was similar for the two drugs suggesting that the variability is due to the animal and not external variables.

Using a Student's *t* test, analysing the average values for each formulation, the differences between the AUC values for test substances A & B are found to be not significant at the 95% confidence level (or at the 90% confidence level). In accord with this there is no consistent trend in these values for individual horses.

Using a non-parametric test, which concentrates on the differences for individual horses, the differences are also not significant. Emphasising this are the mode for the differences which is -47, very close to zero, and the fact that for four horses the difference is positive and for four it is negative.

Thus, the results are consistent with the two formulations delivering the same amount of active agent.

The activity of the product is dependent on the amount of active ingredient that is absorbed by the horse. As the same amount of the active ingredient is absorbed, the pharmacological activity of the two formulations is equivalent.

The lack of a statistical significance between the AUC for each formulation means that the products are bioequivalent.

3.1 AUC results

Horse Number	AUC for A	AUC for B	Difference
1	9829	3486	6343
2	2306	2023	283
3	5689	2412	3277

4	1613	2067	-454
5	6584	8188	-1604
6	1182	1199	-17
7	966	1042	-76
8	1749	1725	24
Mean (SD)	3740 (3246)	2768 (2317)	

3.2 Student's t Test

Unpaired *t* test

Are the means of AUC A and AUC B equal?

Mean difference = -971.75 (Mean of AUC A minus mean of AUC B)

The 95% confidence interval of the difference: -3996.2 to 2052.7

$t = 0.6892$ with 14 degrees of freedom.

The two-tailed *P* value is 0.5020, considered not significant.

Test: Are the standard deviations equal?

The *t* test assumes that the columns come from populations with equal SDs.

The following calculations test that assumption.

$F = 1.962$

The *P* value is 0.1969.

This test suggests that the difference between the two SDs is not significant.

3.3 Summary of Data

Parameter:	AUC A	AUC B
Mean:	3739.8	2768.0
# of points:	8	8
Std deviation:	3245.8	2317.3
Std error:	1147.6	819.28
Minimum:	966.00	1043.0
Maximum:	9829.0	8188.0

Median:	2027.5	2045.0
Lower 95% CI:	1025.8	830.40
Upper 95% CI:	6453.7	4705.6

3.4 Non-parametric Test

Wilcoxon Signed Ranks Test

Ranks

		N	Mean Rank	Sum of Ranks
AUCOLD - AUCNEW	Negative Ranks	3[a]	5.67	17.00
	Positive Ranks	5[b]	3.80	19.00
	Ties	0[c]		
	Total	8		

a. AUCOLD < AUCNEW

b. AUCOLD > AUCNEW

c. AUCNEW = AUCOLD

Test Statistics [b]

	AUCOLD - AUCNEW
Z	-.140[a]
Asymp. Sig. (2-tailed)	.889

a. Based on negative ranks.

b. Wilcoxon Signed Ranks Test

NEW = Test Substance A

OLD = Test Substance B

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In the claims which follow and in the preceding description of the invention, except where the context requires otherwise due to express language or necessary implication, the word "comprise" or variations such as "comprises" or "comprising" is used in an inclusive sense, i.e. to specify the presence of the stated features but not to preclude the presence or addition of further features in various embodiments of the invention.

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. A pharmaceutical composition comprising a metal complex of a carboxylate having anti-inflammatory activity in a pharmaceutically acceptable carrier, wherein

(1) the composition has a colloidal structure, or forms a colloidal structure when administered to a human or animal, or is immiscible with water;

(2) more than 80% of the total amount of the carboxylate having anti-inflammatory activity in the composition is present as part of a metal complex; and

(3) less than 10% of the carboxylate having anti-inflammatory activity complexed with the metal dissociates from the metal over 12 months when the composition is stored in the absence of light at room temperature;

but excluding compositions comprising a complex containing the ligand DMF.

2. A pharmaceutical composition according to claim 1, wherein less than 10% of the carboxylate having anti-inflammatory activity complexed with the metal dissociates from the metal over 18 months when the composition is stored in the absence of light at room temperature.

3. A pharmaceutical composition according to claim 1, wherein less than 5% of the carboxylate having anti-inflammatory activity complexed with the metal dissociates from the metal over 18 months when the composition is stored in the absence of light at room temperature.

4. A pharmaceutical composition according to any one of claims 1 to 3, wherein the carboxylate having anti-inflammatory activity is a NSAID.

5. A pharmaceutical composition according to any one of claims 1 to 4, wherein the metal is Cu, Zn, Co or Ni.

6. A pharmaceutical composition according to any one of claims 1 to 5, wherein the complex is selected from the group consisting of:

$[Cu_2(Asp)_4]$,

$[Cu(Asp)_2L_2]$ where each L is independently selected and is benzimidazole, 2-methylbenzimidazole, metronidazole, 2-methylimidazole, 1,2-dimethylimidazole, pyridine, 3-picoline, 4-picoline, imidazole, 1-methylimidazole, diethylamine,

nicotinamide, or *N*, *N*-dimethylsulfoxide, $[Cu_2(Sup)_4(CH_3CN)_2]$,

$[Cu_2(Sup)_4(OH_2)_2]$,

$[Cu(Tol)_2(pyridine)_2]$,

$[Cu_2(Tol)_4(dmso)_2]$,

$[Cu(Nap)_2(pyridine)_2]$,

$[Cu_2(Nap)_4(dmso)_2]$,

$[Cu(Ibu)_2(pyridine)_2]$,

$[Cu_2(Ibu)_4(dmso)_4]$,

$[Cu(Ibu)_2(imidazole)_2]$,

$[Cu(Ibu)_2(2\text{-methylimidazole})_2]$,

$[Cu_2(Ibu)_4(caffeine)_2]$,

$[Cu_2(Ibu)_4(metronidazole)_2]$,

$[Cu_2(Flufen)_4L_2]$ where each L is independently selected and is caffeine or papaverine,

$[Cu(Flufen)_2L_2]$ where each L is independently selected and is nicotine, nicotinamide or *N,N*-diethylnicotinamide,

$[Cu(Nif)_2L_2]$ where each L is independently selected and is 3-pyridylmethanol or water,

$[Cu_2(Nif)_4(dmso)_2]$,

$[Cu_2(Indo)_4L_2]$ where each L is independently selected and is water, *N,N*-dimethylacetamide, *N*-methyl-2-pyrrolidone, tetrahydrofuran, acetonitrile, acetone or dimethylsulfoxide,

$[Cu_2(Dic)_4L_2]$ wherein each L is independently selected and is water, ethanol, dimethylsulfoxide or methanol,

$[Cu(tenox)_2(py)_2]$.EtOH,

$[Cu_2(Indo)_4(OH_2)_2].nH_2O$; and

mixtures thereof.

7. A pharmaceutical composition according to any one of claims 1 to 6, wherein the composition has a colloidal structure selected from micelles in an aqueous carrier or an oil-in-water emulsion.

8. A composition for oral administration comprising a metal complex of a NSAID, one or more pharmaceutically acceptable oils and one or more pharmaceutically acceptable surfactants, wherein

(1) the one or more oils and one or more surfactants are present in the composition in amounts such that following oral administration of the composition to a human or animal, the composition forms an oil-in-water emulsion on contact with aqueous fluids in the digestive system of the human or animal;

(2) more than 80% of the total amount of the carboxylate having anti-inflammatory activity in the composition is present as part of a metal complex; and

(3) less than 10% of the carboxylate having anti-inflammatory activity complexed with the metal dissociates from the metal over 12 months when the composition is stored in the absence of light at room temperature;

but excluding compositions comprising a complex containing the ligand DMF.

9. A composition according to claim 8 wherein the one or more oils is a medium chain triglyceride.

10. A composition according to claim 8 wherein the one or more surfactants is selected from the group consisting of Sorbitan Fatty Acid Esters surfactants and Caster Oil Polyoxyethylene surfactants.

11. A pharmaceutical composition comprising:

Ingredient:	Amount (% by weight):
One or more metal complexes of a NSAID	3 to 7
One or more glycofurols	30 ± 10%
One or more surfactants	10 ± 10%
One or more thickener	.5 ± 10%
Medium chain triglyceride	50% ± 10%

12. A method for treating an inflammatory condition in a human or animal, the method comprising administering to the human or animal a therapeutically effective amount of a composition according to any one of claims 1 to 11.

Dated this 30th day of March 2004
THE UNIVERSITY OF SYDNEY
By its Patent Attorneys
GRIFFITH HACK

COMS ID No: SMBI-00688319 Received by IP Australia: Time (H:m) 18:00 Date (Y-M-d) 2004-03-30

Figure 1

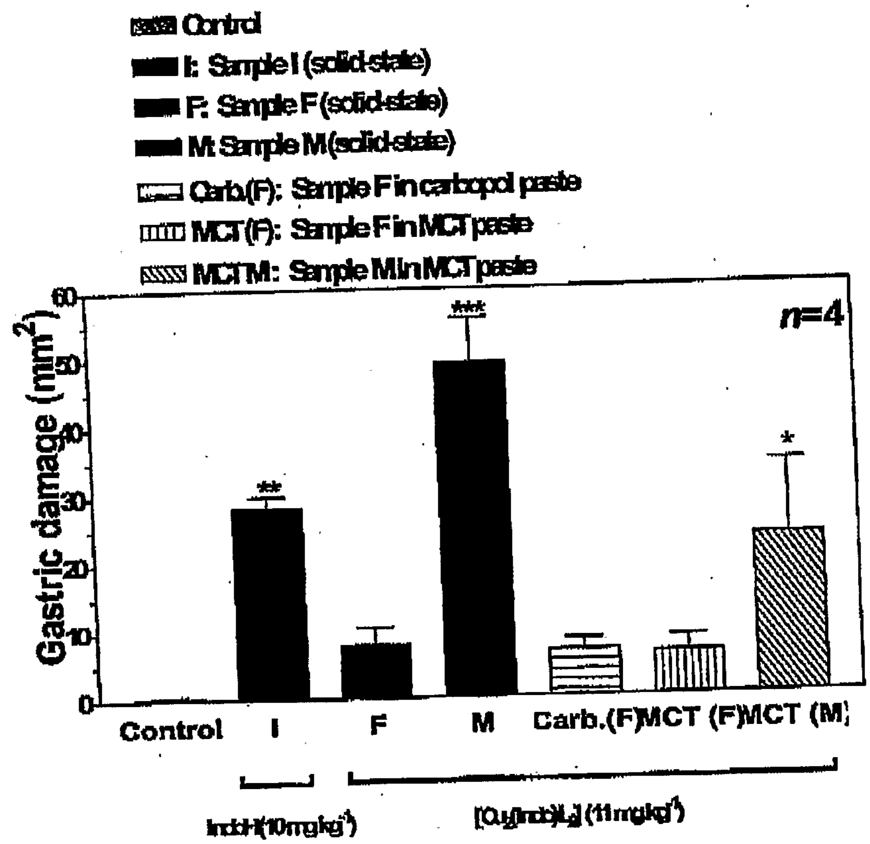
Control
I: Sample I (solid-state)
F: Sample F (solid-state)
M: Sample M (solid-state)
Carb.(F): Sample F in carbopol paste
MCT(F): Sample F in MCT paste
MCT(M): Sample M in MCT paste
n=4
Gastric damage (mm^2)
0
10
20
30
40
50
60
Control
I
F
M
Carb.(F)
MCT (F)
MCT (M)
**
***
*

Figure 2

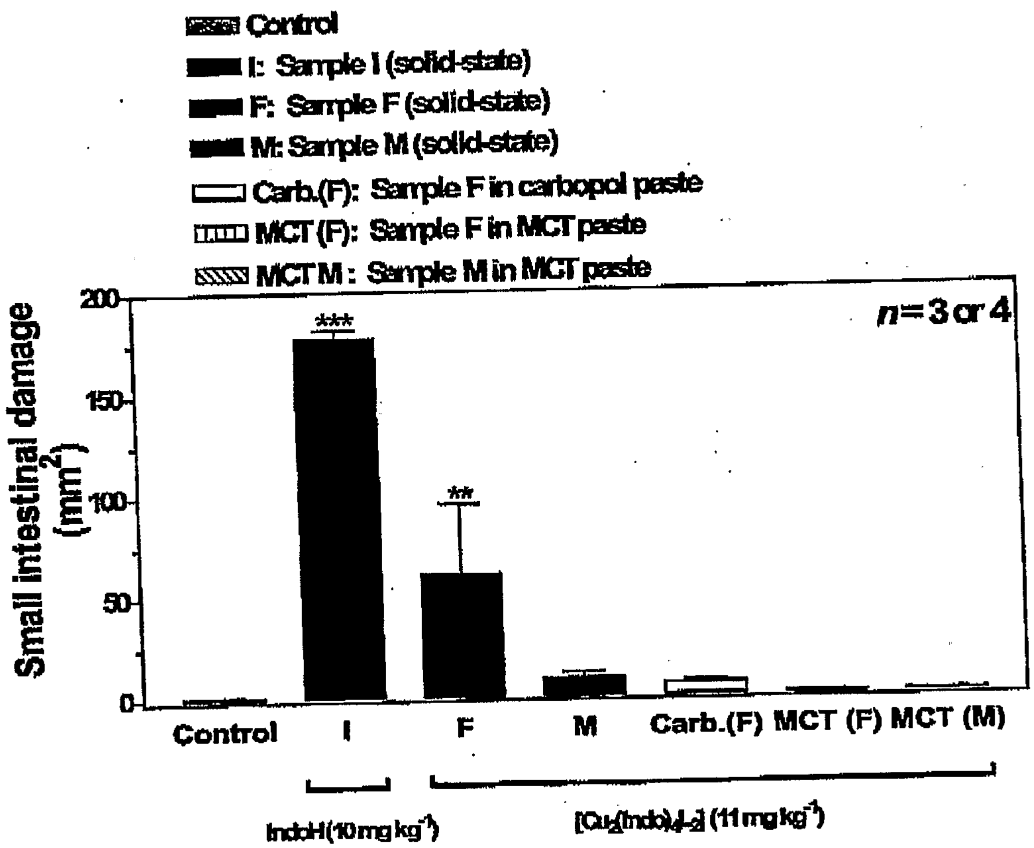

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Figure 3

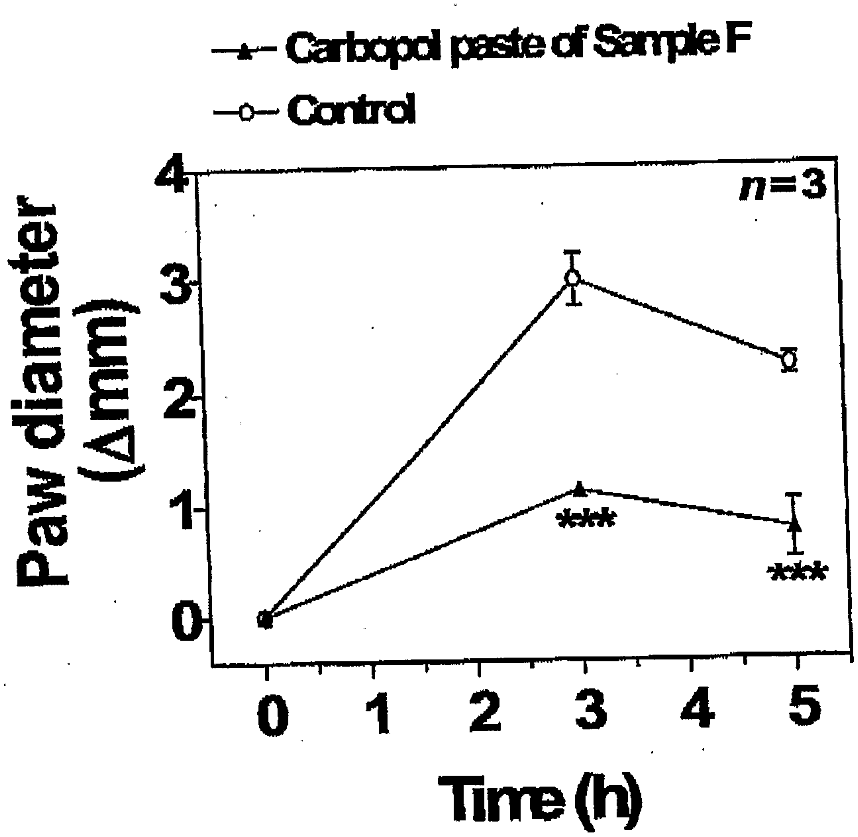

Carbopol paste of Sample F
Control
n=3
Paw diameter (Δmm)
***
***
0
1
2
3
4
0
1
2
3
4
5
Time (h)

Figure 4

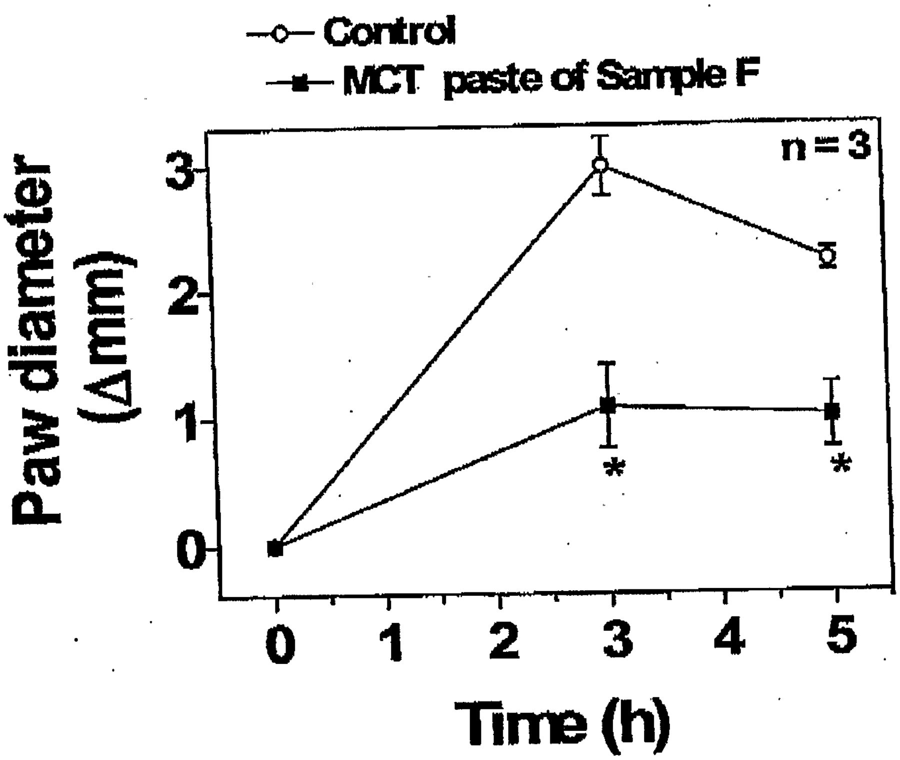

Control
MCT paste of Sample F
n=3
Paw diameter (Δmm)
0
1
2
3
*
*
0
1
2
3
4
5
Time (h)

Figure 5

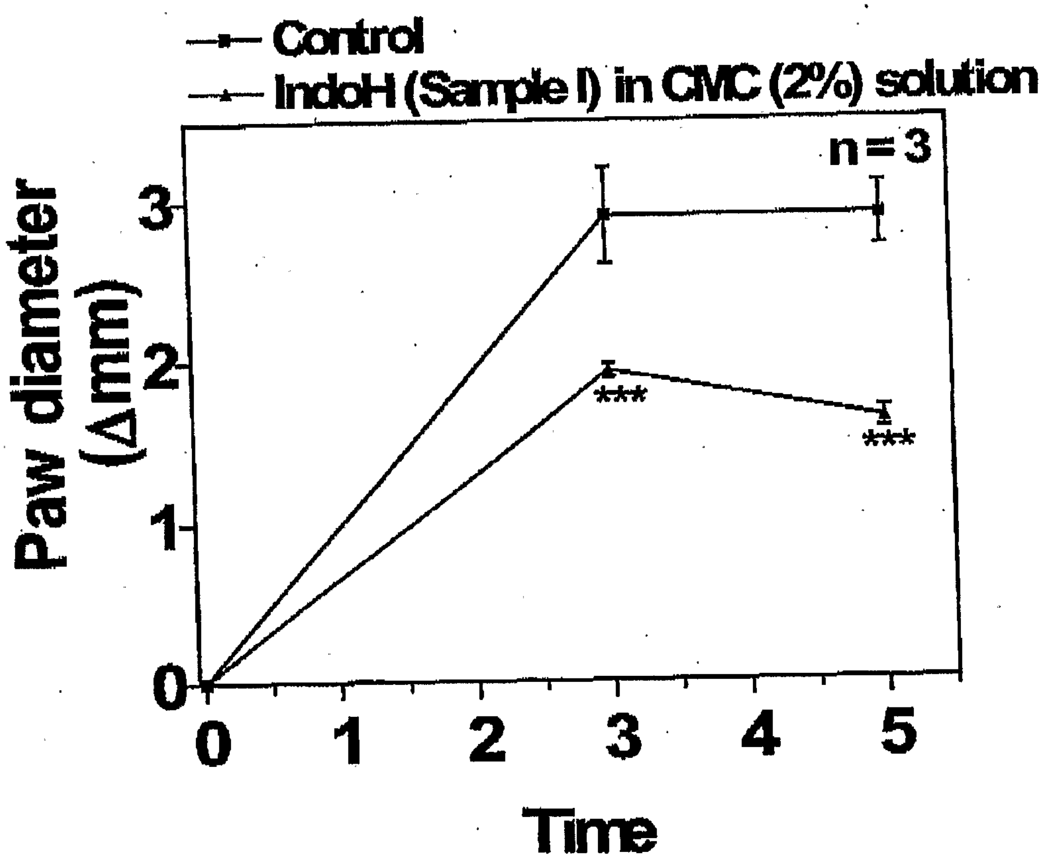
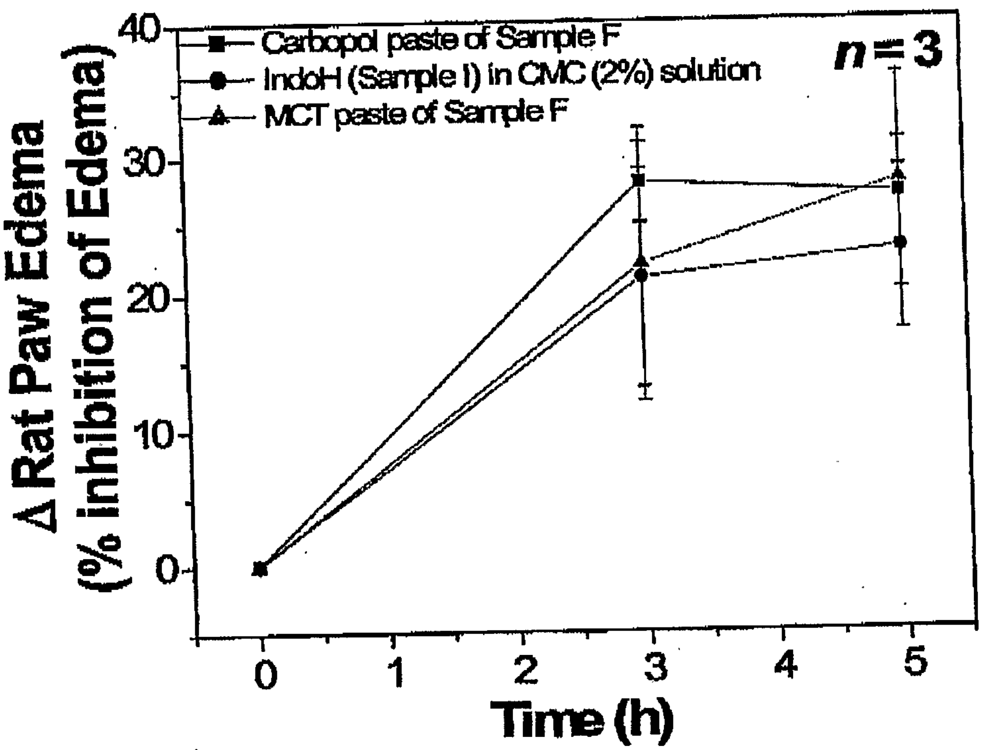

Control
IndoH (Sample I) in CMC (2%) solution
n = 3
Paw diameter (Δmm)
0
1
2
3
***
***
0
1
2
3
4
5
Time

Figure 6


Carbopol paste of Sample F
IndoH (Sample I) in CMC (2%) solution
MCT paste of Sample F
n = 3
Δ Rat Paw Edema
(% inhibition of Edema)
Time (h)
40
30
20
10
0
0
1
2
3
4
5